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Synthesis of *N*-*Z*, *N*′-Formyl α-Amino Acid Derived Gem-Diamines

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Abstract A variety of *N*-carbobenzoxy, *N*′-formyl *gem*-diaminoalkyl derivatives have been obtained through Goldsmith-Wick reaction of Z-α-amino acid/peptide acid derived isocyanates with 96% HCOOH in presence of 4-dimethylaminopyridine (DMAP) as catalyst. The reaction proceeds to completion within 2–4 h and results in good yields of the products isolated as stable solids.

Keywords Z-α-amino acids · Acyl azides · Isocyanates · DMAP · Goldsmith-Wick reaction · Formylation · *Gem*-diamines

Introduction

Formamides are medicinally and synthetically useful class of compounds. They form precursors for the preparation of wide range of important organic compounds like formamidines, monomethylated amines, nitrogen containing hetrocycles and in Vielsmier formylation reactions. As catalysts, they are employed in asymmetric allylations and hydrosilylation of carbonyl compounds. *N*-Formyl amino acid esters are employed in enzymatic synthesis of peptides in aqueous media. The formyl group also serves as an effective *N* as well as *O* protecting group (Sarvari and Sharghi 2006). They are dehydrated to isonitriles which form starting materials for 1-substituted tetrazoles, oxazolines, pyrroles and are the key components in Passerini and Ugi's multi component reactions (Domling and Ugi 2000). Synthesis of partially modified retroinverso peptides (PMRIs) using *N*-formyl protected amino acids has also been explored (Chorev and Goodman 1983; Chorev 2005).

The conversion of amino group of amino acid ester into formamide results in the *N*-formylated amino acid derivative as shown in the Fig. 1. A large number of efficient protocols have been reported for achieving this type of transformation. On the other hand, *N*-formamide group can also be inserted in the place of α-carboxyl group of *N*-protected amino acid. Since formamide group is the derivative of amine, a synthesis of this kind can be visualized possible in view of the availability of methods for converting the –COOH group into amine through Curtius or Hoffmann rearrangement (Fletcher and Campbell 1998). Derivatization of the newly obtained amine with formic acid leads to functionalized formamides (Fig. 2), a useful class of synthons. They are employable as starting materials to access synthetically valuable *N*-urethane protected compounds, for instance, urethane protected α-amino isonitriles.

The reported protocols for converting the α-amino group into formamide moiety include reacting the amines directly with formic acid or in presence of a catalyst like ZnO and formylating agents like KF-Al_2O_3, chloral, acetic formic anhydride, activated formic acid using DCC/EDC, formic acid esters, ammonium formates, 2-chloro-4,6-dimethoxy[1,3,5] triazole (CDMT), cyanomethyl formate and supported reagents (Sarvari and Sharghi 2006).

Nevertheless, there were no reports in the literature (Scheibler and Chorev 2003) concerning to the conversion of carboxyl group of *N*-protected amino acid into the corresponding formamide moiety until our group recently published a note on the synthesis of *N*-Fmoc,*N*′-formyl *gem*-diaminoalkyl derivatives from Fmoc amino acids

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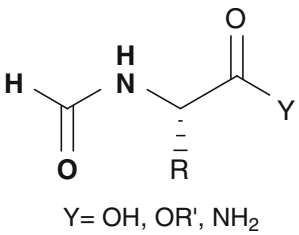


Fig. 1 *N*-Formyl amino acid ester

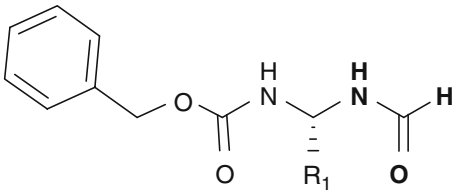


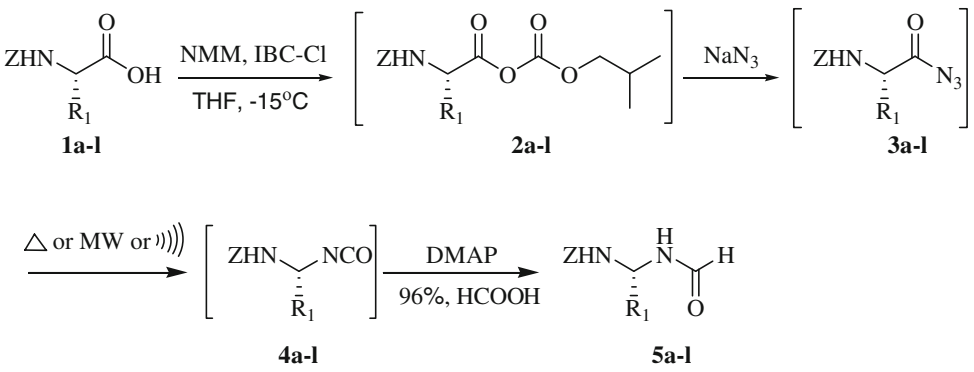
Fig. 2 *N*-Benzyloxycarbonyl, *N*′-formyl *gem*-diamine

(Sudarshan et al. 2007). The synthesis of such compounds would require generation of a *gem*-diamine (Fuller et al. 1985) precursor through any of the known methods (Fletcher and Campbell 1998) and then reacting with suitable formylating agent. But since the alkyl *gem*-diamines are known to decompose into amides, aldehydes and amines (Loudon et al. 1981; Parham and Loudon 1978) and are difficult to prepare in good yields, an alternate route devoid of the generation of *gem* diamine is required.

The synthesis of the related *N*-formylated *gem* diamines particularly useful as intermediates for PMRIs has been reported (Chorev and Goodman 1983; Berman and Goodman 1984). This synthesis employs *N*-formyl protected α-amino acids as starting materials and converts them into corresponding acyl azides followed by the rearrangement of the latter into isocyanates. The *N*-formyl α-amino-isocyanates are then trapped with benzyl alcohol or tert-butyl alcohol to yield *N*-formyl, *N*′-benzyloxycarbonyl or tert-butyloxycarbonyl *gem* diamines. But in our hands, coupling of alcohols to isocyanates was slow and required long hours of reflux or microwave acceleration (Venkataramanarao et al. 2007). In contrast, formylation of isocyanates *via* Goldsmith-Wick reaction was recently reported to take place rapidly in the presence of 4-dimethylaminopyridine (DMAP) and at 0°C and offers practically attractive route to access the title compounds (Schuemacher and Hoffmann 2001). However, Goodman and co-workers have thoroughly studied the usage of urethane protected aminoisocyanates as synthetic intermediates and have shown that they are prone to multiple side reactions essentially arising from the heterolytic cleavage of C-NCO bond in polar solvent (Chorev 1984). Pallai and co-workers have reported similar results on the instability of urethane protected *gem*-diamines obtained from the oxidative rearrangement of corresponding amides (Pallai 1983). Despite this, we envisioned that unlike the alcoholysis of the isocyanates under high temperature reflux and highly polar methanolic reaction medium, as described by Goodman et al., Goldsmith-Wick formylation proceeds under very mild reaction conditions and in non-polar CH_2Cl_2 solvent and hence would minimize the likely side reactions of urethane protected aminoisocyanates. Also in recent years, the synthetic utility of *N*-Fmoc/Boc/Z-protected isocyanates is being explored with respect to the preparation of peptidomimetics.

In this context, we proceeded with the direct reaction of Z-α-amino-isocyanates with formic acid. Z group was selected in view of its practical utility for solution phase peptide synthesis when compared with Fmoc-chemistry. It enables the deprotection employing catalytic hydrogenation under neutral conditions thus circumventing the acid catalyzed degradation of *gem*-diamines. We report in this paper an efficient synthesis of *N*-formyl, *N*′-benzyloxycarbonyl gem-diamines by the reaction of Z-α-amino isocyanates with formic acid (Scheme 1).

The synthetic utilities of *N*-urethane protected α-amino-isocyanates in the preparation of peptidomimetics have been documented in the literature. Isocyanates derived from azides of *N* protected amino acids and peptide acids have been employed in synthesis of peptidomimetics like peptidyl ureas (Patil et al. 2003; Sureshbabu et al. 2006) and PMRIs. Fischer et al., recently reported the conversion of a series of Z-α-amino isocyanates into active *N*-hydroxy succnimidyl carbamates employed as building blocks to assemble ureidodipeptides (Fischer et al. 2007). Venkataramanarao and Sureshbabu have described the synthesis of Fmoc protected



Scheme 1 Synthesis of *N*-formylated gem-diamines from Z-amino acids

PMRIs by reacting the isocyanates derived from Fmoc-amino acids with Boc/Z- amino acids in presence of DMAP through Goldsmith-Wick reaction (Venkataramanarao and Sureshbabu 2006). Herein we present a novel and useful application of Z-α-amino acid derived isocyanates through the synthesis of the title functionalized formamides.

Materials and Methods

The amino acids were obtained from Sigma-Aldrich Company. Melting points were determined using capillary method and are uncorrected. LG domestic microwave oven (LG MS 194A) operating at 2,450 MHz was used for the preparation of isocyanates. Ultrasonication under TRANSSONIC T 310/H Ultrasonic bath, IR spectra were recorded on a Nicolet model impact 400D FT-IR spectrometer (KBr pellets, 3 cm^{-1} resolution), ^1H NMR spectra were recorded on a Bruker 400 MHz. Mass spectra were recorded on ES-MS (HP 1100 series, MSD single quadrapole). The TLC was effected with silica gel *GF254* obtained from MERCK Chemicals on pre-coated glass plates using as mobile phases the following solvent systems: (a) chloroform:methanol (9:1) and (b) ethyl acetate:hexane (6:4). All solvents were freshly distilled prior to use. The N^{α}-Z-dipeptide acids were prepared *via* mixed anhydride method by employing *O*,*N*-bis-trimethylsilyl amino acids using the reported procedures (Tantry and Sureshbabu 2004). All the six Z-peptides made were purified and characterized prior to use.

Characterization data of Z-dipeptide acids

Z-Ala-Val-OH: M.p 97°C; ^{1}HNMR ($CDCl_3$):-1.10 (d, 6H), 1.51 (d, 3H), 2.62 (m, 1H), 4.59 (m, 1H), 4.73 (m, 1H), 5.42 (s, 2H), 6.58 (m, 1H), 7.12–7.25 (m, 5H), 7.53 (m, 1H); ^{13}CNMR:- 17.8, 18.1, 35.3, 52.3, 60.5, 68.2, 128.5, 129.2, 131.0, 149.3, 154.9, 175.9, 178.9.

Z-Leu-Val-OH: M.p 82°C; ^{1}HNMR ($CDCl_3$):- 0.94–1.10 (m, 12H), 1.81 (m, 1H), 1.91 (m, 1H), 2.17 (m, 1H), 4.39 (m, 1H), 4.42 (m, 1H), 5.40 (s, 2H), 6.61 (m, 1H), 7.12–7.25 (m, 5H), 7.49 (m, 1H); ^{13}CNMR:- 17.6, 21.3, 22.9, 34.8, 41.8, 52.3, 61.1, 69.0, 128.3, 128.9, 131.5, 148.1, 155.2, 175.3, 178.9.

Z-Phe-Ala-OH: M.p 158°C; ^{1}HNMR ($CDCl_3$):- 1.31 (d, 3H), 2.8–3.2 (m, 2H), 4.81 (m, 1H), 5.12 (m, 1H), 5.30 (s, 2H), 6.41 (m, 1H), 7.10–7.36 (m, 10H), 7.51 (m, 1H); ^{13}CNMR:- 17.0, 36.2, 52.5, 60.8, 68.8, 125.3, 126.1, 126.8, 128.3, 129.1, 130.9, 139.8, 149.1, 155.0,175.1, 178.0.

Z-L-Phg-Ala-OH: M.p168°C; ^{1}HNMR ($CDCl_3$):- 1.29 (d, 3H), 4.71 (m, 1H), 5.29 (s, 2H), 5.91 (s, 1H), 6.68 (m, 1H), 7.10–7.40 (m, 10H), 7.48 (m, 1H); ^{13}CNMR:- 17.1, 52.9, 60.8, 68.3, 127.1, 128.3, 128.9, 129.2, 129.8, 131.5, 137.1, 149.8, 155.8, 175.8, 178.5.

Z-D-Phg-Ala-OH: M.p 114°C; ^{1}HNMR ($CDCl_3$):- 1.32 (d, 3H), 4.71 (m, 1H), 5.29 (s, 2H), 5.91 (s, 1H), 6.68 (m, 1H), 7.10–7.40 (m, 10H), 7.48 (m, 1H); ^{13}CNMR:- 17.3, 53.0, 60.8, 68.1, 127.2, 128.5, 129.1, 129.3, 129.8, 131.2, 137.0, 150.0, 155.8, 175.8, 178.6.

Z-Pro-Val-OH: M.p 130°C; ^{1}HNMR ($CDCl_3$):- 1.12 (d, 6H), 1.29–1.52 (m, 4H), 2.68 (m, 1H), 3.41 (m, 2H), 4.35 (m, 1H), 4.56 (m, 1H), 5.38 (s, 2H), 6.78 (m, 1H), 7.15–7.27 (m, 5H), 7.51 (m, 1H); ^{13}CNMR:- 17.4, 22.9, 28.9, 30.9, 47.3, 52.6, 61.0, 69.2, 128.0, 128.3, 130.9, 148.7, 155.9, 175.2, 178.8.

Typical procedure for the preparation of *N*-Benzyloxycarbonyl, *N*′-formyl-alkane-1,1-diamines

To a stirred solution of Z-amino acid/peptide acid (10 mmol) in dry THF at −10°C, was added NMM (1.1 ml, 10 mmol) and ethyl chloroformate (0.91 ml, 10 mmol) and stirring continued for another 20 min at the same temperature, then sodium azide (0.96 g, 15 mmol) in water (0.5 ml) was added and stirred at 0°C for 20 min. The reaction mixture was evaporated at room temperature under reduced pressure. The residue was diluted with dichloromethane, washed with 10% $NaHCO_3$ (10 ml), 10% citric acid (10 ml) and water (10 ml × 2). The organic layer was dried over sodium sulphate and concentrated to yield respective azides.

Further, the azide was dissolved in minimum quantity of toluene (5 ml) and exposed to microwave irradiation at 60% total power output of the instrument for one minute or subjected to ultrasonication at room temperature for 15–20 min or refluxed for 30 min to obtain the isocyanate. After the removal of excess toluene, the residue was diluted with dry DCM and cooled to 0°C. To this, DMAP (0.12 g, 1.0 mmol) was added followed by 96% HCOOH (0.57 ml, 15 mmol) and stirring continued at the same temperature till the completion of the reaction as evident by precipitation of the product within 2–4 h. The reaction mixture was diluted with 15 ml each of water and hexane and the precipitated solid was filtered, washed with ether, 10% $NaHCO_3$, 10% citric acid and water. The compound was dried under suction and was recrystallized using dichloromethane: hexane to obtain the product.

Characterization Data for *N*-Benzyloxycarbonyl-*N*′-Formylalkane-1,1-Diamines **5a–k**

1. ***N*-Benzyloxycarbonyl-*N*′-formylmethanediamine (Z-*g*Gly-For, 5a):** IR (KBr): 1,655 and 1,710 cm^1; R_f (10% MeOH/$CHCl_3$): 0.30; ^{1}H NMR (δ, DMSO): 4.26 (m, 2H), 4.99 (s, 2H), 7.28 (m, 5H), 7.96 (s, 1H), 8.03 (m, 1H); ^{13}C NMR (δ, DMSO): 56.53, 64.10, 127.58, 127.70, 128.24, 136.36, 159.80, 165.49.

2. **(*S*)-*N*-Benzyloxycarbonyl-*N′*-formylethane-1, 1-diamine (Z-*g*Ala-For, 5b):** IR (KBr): 1,658 and 1,712 cm^1; R_f (10% MeOH/$CHCl_3$): 0.32; ^{1}H NMR (δ, DMSO): 1.15 (d, 3H, J = 6.8 Hz), 5.01 (s, 2H), 5.19 (m, 1H), 7.27 (m, 5H) 7.96 (s, 1H), 8.05 (m, 1H), 8.32 (m, 1H); ^{13}C NMR (δ, DMSO): 20.83, 56.48, 63.40, 127.71, 128.40, 137.40, 159.90, 164.12.
3. **(*S*)-*N*-Benzyloxycarbonyl-*N′*-formyl-2-phenylethane-1,1-diamine (Z-*g*Phe-For, 5c):** IR (KBr): 1,658 and 1,705 cm^1; R_f (10% MeOH/$CHCl_3$): 0.30; ^{1}H NMR (δ, DMSO): 2.91 (d, 2H, J = 7.2 Hz) 4.98 (s, 2H), 5.61 (m, 1H), 7.01–7.52 (m, 10H) 7.95 (s, 1H), 8.01 (m, 1H), 8.21 (m, 1H); ^{13}C NMR (δ, DMSO): 37.41, 54.61, 66.64, 127.12, 127.18, 127.81, 128.24, 128.41, 131.56, 137.40, 159.70, 164.02.
4. **(*S*)-*N*-Benzyloxycarbonyl-*N′*-formyl-2-methylpropane-1,1-diamine (Z-*g*Val-For, 5d):** IR (KBr): 1,660 and 1,710 cm^1; R_f (10% MeOH/$CHCl_3$): 0.32; ^{1}H NMR (δ, DMSO): 0.96 (d, 6H, J = 7.1 Hz), 1.91 (m, 1H), 5.00 (s, 2H), 5.21 (m, 1H), 7.26 (m, 5H), 8.11 (br, 1H), 7.96 (s, 1H), 8.11 (m, 1H), 8.18 (m, 1H); ^{13}C NMR (δ, DMSO): 18.40, 31.72, 61.62, 65.68, 127.70, 128.40, 136.40, 155.36, 164.12.
5. **(*S*)-*N*-Benzyloxycarbonyl-*N′*-formyl-3-methylbutane-1,1-diamine (Z-*g*Leu-For, 5e):** IR (KBr): 1,659 and 1,705 cm^1; R_f (10% MeOH/$CHCl_3$): 0.31; ^{1}H NMR (δ, DMSO): 0.95 (d, 6H, J = 5.9 Hz), 1.51–1.82 (m, 3H), 4.95 (s, 2H), 5.05 (m, 1H), 7.27 (m, 5H), 7.96 (s, 1H), 8.12 (br, 1H), 8.23 (m, 1H); ^{13}C NMR (δ, DMSO): 25.31, 35.60, 57.21, 66.68, 127.69, 128.36, 137.34, 155.12, 164.22.
6. **(S)-*N*-Benzyloxycarbonyl-*N′*-formyl-2-methylbutane-1,1-diamine (Z-*g*Ile-For, 5f):** IR (KBr): 1,655 and 1,708 cm^1; R_f (10% MeOH/$CHCl_3$): 0.30; ^{1}H NMR (δ, DMSO): 0.82 (m, 6H), 1.01–1.85 (m, 3H), 4.99 (s, 2H), 5.16 (m, 1H), 7.26 (m, 5H), 7.92 (s, 1H), 8.10 (br, 1H), 8.21 (br, 1H); ^{13}C NMR (δ, DMSO): 10.98, 14.38, 24.78, 38.89, 59.22, 65.41, 127.71, 128.34, 137.20, 160.51, 164.66.
7. **(*S*)-*N*-Benzyloxycarbonyl-*N′*-formyl-phenylmethane-1,1-diamine (Z-L-*g*Phg-For, 5h):** IR (KBr): 1,662 and 1,710 cm^1; R_f (10% MeOH/$CHCl_3$): 0.29; ^{1}H NMR (δ, DMSO): 5.00 (s, 2H), 6.20 (m, 1H), 7.10–7.45 (m, 10H), 7.93 (s, 1H), 8.11 (m, 1H), 8.20 (br, 1H); ^{13}C NMR (δ, DMSO): 59.59, 69.11, 123.95, 125.30, 127.71, 128.34, 128.96, 135.01, 137.15, 159.32, 162.21.
8. **(R)-*N*-Benzyloxycarbonyl-*N′*-formyl-phenylmethane-1,1-diamine (Z-D-*g*Phg-For, 5i):** IR (KBr): 1,657 and 1,710 cm^1; R_f (10% MeOH/$CHCl_3$): 0.29, ^{1}H NMR (δ, DMSO): 5.01 (s, 2H), 6.22 (m, 1H), 7.10–7.50 (m, 10H), 7.95 (s, 1H), 8.10 (m, 1H), 8.22 (br, 1H); ^{13}C NMR (δ, DMSO): 59.61, 69.15, 123.94, 125.32, 127.73, 128.35, 128.96, 135.05, 137.15, 159.31, 162.29.
9. **(*S*)-*N*-Benzyloxycarbonyl-*N′*-formyl-3-methylthiopropane-1,1-diamine (Z-*g*Met-For, 5g):** IR (KBr): 1,658 and 1,715 cm^1; R_f (10% MeOH/$CHCl_3$): 0.30; ^{1}H NMR (δ, DMSO): 2.03 (s, 3H), 2.14 (m, 2H), 2.40 (m, 2H), 5.00 (s, 2H), 5.15 (m, 1H), 7.20 (m, 5H), 7.95 (s, 1H), 8.09 (m, 1H), 8.20 (m, 1H); ^{13}C NMR (δ, DMSO): 15.26, 16.20, 30.21, 59.64, 66.90, 127.70, 128.38, 137.30, 158.58, 163.22.
10. **(*S*)-Methyl-*N*-benzyloxycarbonyl, *N′*-formyl-3, 3-diaminoproanoate (Z-gAsp-(OMe)-For, 5j):** IR (KBr): 1,659 and 1,710 cm^1; R_f (10% MeOH/$CHCl_3$): 0.29; ^{1}H NMR (δ, DMSO): 2.96 (m, 2H), 3.71 (s, 3H), 5.01 (s, 2H), 5.35 (m, 1H), 7.23 (m, 5H), 7.91 (s, 1H), 8.06 (m, 1H), 8.42 (d, 1H); ^{13}C NMR (δ, DMSO): 40.14, 53.44, 59.60, 65.46, 127.70, 128.36, 137.29, 156.60, 164.10, 169.72.
11. **(*S*)-Methyl-*N*-benzyloxycarbonyl, *N′*-formyl-4,4-diaminobutanoate (Z-gGlu-(OMe)-For, 5j):** IR (KBr): 1,657 and 1,709 cm^1; R_f (10% MeOH/$CHCl_3$): 0.28; ^{1}H NMR (δ, DMSO): 1.82 (m, 2H), 2.66 (m, 2H), 3.72 (s, 3H), 5.00 (s, 2H), 5.32 (m, 1H), 7.21 (m, 5H), 7.94 (s, 1H), 8.03 (m, 1H), 8.39 (d, 1H); ^{13}C NMR (δ, DMSO): 15.90, 30.10, 53.46, 59.62, 65.41, 127.72, 128.34, 137.26, 156.61, 164.12, 169.73.
12. **(*S*)-*N*-Benzyloxycarbonyl-*N′*-formyl-2-benzylthioethane-1,1 diamine (Z-*g*Cys(Bn)-For, 5k):** IR (KBr): 1,659 and 1,710 cm^1; R_f (10% MeOH/$CHCl_3$): 0.30; ^{1}H NMR (δ, DMSO): 3.29 (d, 2H), 3.71 (s, 2H), 5.00 (s, 2H), 5.49 (m, 1H), 7.12–7.50 (m, 10H), 7.95 (s, 1H), 8.18 (m, 1H), 8.65 (br, 1H); ^{13}C NMR (δ, DMSO): 36.64, 37.61, 59.95, 66.96, 127.01, 127.70, 128.30, 128.61, 131.92, 135.03, 137.90, 157.70, 164.61, 175.90.

Spectral Data for Functionalized Formamides **7a–d** Derived from Z-Dipeptide Acids

13. **Benzyl (*S*)-1-[(*S*)-1-formamido-2-methylpropylamino]-1-oxopropan-2-ylcarbama te (Z-Ala-*g*Val-For, 7a):** IR (KBr): 1,655 and 1,705 cm^1; R_f (10% MeOH/$CHCl_3$): 0.24; ^{1}H NMR (δ, DMSO): 0.84 (d, 6H, J = 6.8 Hz), 1.20 (d, 3H, J = 7.0 Hz), 1.99 (m, 1H), 4.15 (m, 1H), 4.98 (s, 2H), 5.28 (m, 1H), 7.28 (m, 5H), 7.96 (s, 1H), 8.15 (m, 1H), 8.41 (m, 1H); ^{13}C NMR (δ, DMSO): 18.09, 20.22, 31.80, 54.40, 61.67, 66.15, 127.21, 127.79, 136.38, 155.61, 163.66, 172.92.

14. **Benzyl (*S*)-2-[(*S*)-1-formamidoethylamino]-2-oxo-1-phenylethylcarbamate (Z-L-Phg-*g*Ala-For, 7b):** IR (KBr): 1,662 and 1,712 cm^1; R_f (10% MeOH/$CHCl_3$): 0.23; ^1H NMR (δ, DMSO): 1.26 (d, 3H, J = 7.6 Hz), 4.61 (m, 1H), 5.00 (s, 1H), 5.21 (m, 1H), 7.27–7.43 (m, 10H), 7.94 (s, 1H), 8.04 (m, 1H), 8.18 (m, 1H); ^{13}C NMR (δ, DMSO): 20.64, 54.44, 57.80, 66.12, 126.34, 127.20, 127.75, 127.81, 130.90, 133.27, 136.20, 155.61, 164.10, 172.
15. **Benzyl (*S*)-1-[(*S*)-1-formamido-2-methylpropylamino]-4-methyl-1-oxopentan-2-ylcarbamate (Z-Leu-*g*Val-For, 7f):** IR (KBr): 1,659 and 1,710 cm^1; R_f (10% MeOH/$CHCl_3$): 0.23; ^1H NMR (δ, DMSO): 0.90 (m, 12H), 1.51–2.30 (m, 4H), 3.88 (m, 1H), 4.95 (s, 2H), 5.25 (m, 1H), 7.27 (m, 5H), 7.94 (s, 1H), 8.08 (m, 1H), 8.18 (m, 1H); ^{13}C NMR (δ, DMSO): 18.44, 25.30, 31.71, 35.60, 51.44, 57.780 127.20, 128.81, 136.36, 156.30, 164.10, 172.29.
16. **Benzyl 2-{[(*S*)-1-formamido-2-methylpropyl]carbamoyl}pyrrolidine-1-carboxyla te (Z-Pro-*g*Val-For, 7d):** IR (KBr): 1,659 and 1,710 cm^1; R_f (10% MeOH/$CHCl_3$): 0.24; ^1H NMR (δ, DMSO): 0.73 (d, 6H, J = 7.4 Hz), 1.77 (br, 4H), 1.86 (m, 1H), 3.34 (m, 2H), 4.18 (m, 1H), 4.96 (s, 2H), 5.20 (m, 1H), 7.27 (m, 5H), 7.95 (s, 1H), 8.05 (m, 1H), 8.32 (m, 1H); ^{13}C NMR (δ, DMSO): 18.45, 23.80, 28.71, 31.71, 46.90, 54.44, 61.19, 67.15, 127.80, 128.88, 128.45, 136.99, 155.45, 164.20, 173.21.

Results and Discussions

In a typical reaction Z-Ala-OH, **1b** was converted into its corresponding acid azide on treatment of its mixed anhydride **2b** with sodium azide. The azide **3** was subjected to Curtius rearrangement following any one of the methods: thermal (Chorev et al. 1977; Patil et al. 2003) or irradiation using microwaves or subjecting to ultrasonication (Sureshbabu et al. 2005) to accomplish the conversion in to isocyanate **4b**. Complete conversion into isocyanate was confirmed by the disappearance of the azide peak at 2,110 cm^{-1} and the appearance of a distinct isocyanate peak at 2,230 cm^{-1} in IR analysis. The dichloromethane solution of **4b** was then treated with 96% formic acid in presence of catalytic amount of DMAP at 0°C and the reaction was continued until completion by monitoring through TLC. The desired functionalized formamide **5b** conveniently precipitated from the reaction mixture. The addition of DMAP to the isocyanate solution was done in the view of the known activation of isocyanate towards the attack by the carbonyl oxygen upon complexation with DMAP (Schuemacher and Hoffmann 2001). Further the requirement of DMAP to drive the reaction was evident when the uncatalyzed reaction showed very less formation of the product even with higher equivalents of formic acid. As a catalyst, DMAP was meritorious over the other tertiary amines like *N*-methylmorpholine (NMM), triethyl amine (TEA) and pyridine as these resulted in lesser yields even with higher equivalents. Increase of temperature to 25 °C also resulted in lesser yields due to the formation of mixture of impurities. Employing this protocol (Scheme 1), a variety of isocyanates derived from Z-amino acids was converted to related formamides **5a–l** on a 10 mmole scale (Table 1). All the compounds made were obtained in good yield and fully characterized using ^1H NMR, ^{13}C NMR and mass spectrometry.

The protocol was extended to the synthesis of formamides derived from Z-protected peptide acids. The peptide acids were synthesized by coupling with *O,N*-bis-trimethylsilyl amino acid with mixed anhydride of Z-amino acids (Tantry and Sureshbabu 2004). The dipeptide acids were further converted to corresponding isocyanates through the

Table 1 *N*-Benzyloxycarbonyl-N′-formyl-gem-diaminoalkyl derivatives **5a–k** prepared through Scheme 1

Compound	R_1	Yield%	M.p°C	HRMS $[M+Na]^+$ Calc.	HRMS $[M+Na]^+$Observed
5a	H	90	162–63	231.0746	231.0750
5b	CH_3	91	132–33	245.0902	245.0906
5c	$CH_2C_6H_5$	92	174–75	321.1215	321.1213
5d	$CH(CH_3)_2$	90	138–39	273.1215	273.1218
5e	$CH_2CH(CH_3)_2$	85	123–24	287.1372	287.1368
5f	$CH(CH_3)CH_2CH_3$	86	148–49	287.1372	287.1371
5g	C_6H_5 (L)	90	158–59	307.1059	307.1057
5h	C_6H_5 (D)	91	160–61	307.1059	307.1061
5i	$(CH_2)_2SCH_3$	84	150–51	305.0936	305.0933
5j	$CH_2COOCH_2C_6H_5$	80	108–09	379.1270	379.1274
5k	$(CH_2)_2COOCH_2C_6H_5$	78	102–03	393.1426	393.1423
5l	$CH_2SCH_2C_6H_5$	86	140–41	367.1092	367.1094

Scheme 2 Synthesis of *N*-formylated gem-diaminoalkyl derivatives of Z-dipeptides

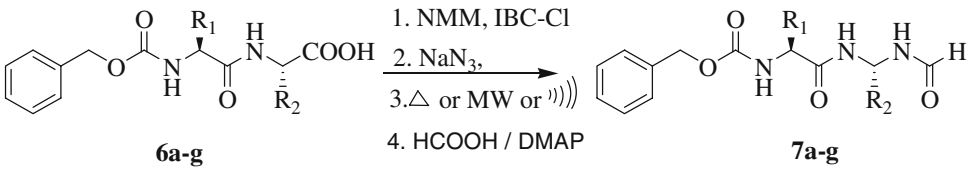


Table 2 *N*-formylated gem-diaminoalkyl derivatives of dipeptides prepared through Scheme 2

Compound	R_1	R_2	Yield %	M.p °C	HRMS $[M+Na]^+$Calc.	HRMS $[M+Na]^+$ Observed
7a	CH_3	$CH(CH_3)_2$	75	150–51	344.1586	344.1589
7b	C_6H_5 (L)	CH_3	78	161–62	378.1430	378.1426
7c	C_6H_5 (D)	CH_3	79	164–65	378.1430	378.1428
7d	$-(CH_2)_3-$	$CH(CH_3)_2$	73	141–44	370.1743	370.1739
7e	$CH_2C_6H_5$	CH_3	81	158–60	392.1586	392.1590
7f	$CH_2CH(CH_3)_2$	$CH(CH_3)_2$	70	133–34	386.2056	386.2053

rearrangements of parent acid azides under reflux or microwave irradiation and reacted with HCOOH in presence of DMAP to obtain the required formamides **7a–f** in good yields (Scheme 2, Table 2).

Epimerization during the course of the reaction was examined by recording the ^{1}H NMR spectrum of crude **7b** and **7c** synthesized using the present method. **7b** contained a doublet at 1.29, 1.31 corresponding to the methyl group protons. While its other epimer, **7c** had the $-CH_3$ doublet at 1.21, 1.22. Furthermore, the equimolar mixture containing **7b** and **7c** had peaks at four different δ values, 1.21, 1.25, 1.29, 1.32. This demonstrated that the proposed procedure was epimerization free.

Conclusions

We have demonstrated that the isocyanate derived from Z-amino acid/peptide acid azides can be used as an easily accessible functionality to generate various *N*-benzyloxycarbonyl *N*′-formyl *gem*-diaminoalkyl compounds. The synthesis involves Curtius rearrangement of Z-α-amino acyl azides into related isocyanate and reaction of the latter with formic acid under DMAP catalysis. The procedure is operationally simple, high yielding and enables formylation of the isocyanates under mild conditions.

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